Remarks

Prior to this Amendment, claims 1-53 were pending. By this Amendment, new claims 54-67 have been added. Accordingly, claims 1-67 are now pending.

Claims 10, 16, 17, 34, 42, and 52 have been amended to recite "the pH of the formulation is about 5.1 when measured as an aqueous slurry." Support for this amendment is found in the specification, at page 10, lines 12-13.

Claim 22 has been amended to simplify the language by deleting the word "further."

Claim 35 has been amended to add a period at the end of the claim and to delete the internal period.

Claims 46-52 have been amended to correct an inadvertent error and now recite "The method of."

New claims 54-67 have been added and recite various pH values. Support for these new claims is found in the specification, at page 10, lines 10-13.

The rejections under 35 U.S.C. §112

Claims 10, 16, 17, 42, and 52 were rejected as being indefinite because the recitation of "pH" was said to have no antecedent basis.

In order for claims 10, 16, 17, 42, and 52 to even more particularly point and distinctly claim the invention, these claims have been amended to recite "the pH of the formulation is about 5.1 when measured as an aqueous slurry." Accordingly, it is respectfully requested that this rejection be withdrawn.

Claim 22 was rejected as being indefinite because of the language "further where."

Claim 22 has been amended to delete the word "further." Accordingly, it is respectfully requested that this rejection be withdrawn.

The rejections under 35 U.S.C. §103(a)

Claims 1-5, 13, 15-24, 26-29, 35, 36, 39, 43, 45-47, and 53 were rejected as being obvious over U.S. Patent No. 6,919,087 (Lemmens).

The Office Action, at page 3, stated:

> [I]t would have been obvious to one of ordinary skill in the art to, by routine experimentation optimize the amlodipine maleate composition taught by Lemmens to eliminate the use of magnesium stearate to obtain the claimed invention, because Lemmens teaches an amlodipine maleate having the claimed impurity in the same storage condition at one month, because Lemmens teaches a pharmaceutical composition that does not comprise magnesium stearate has been shown to provide good stability against the formation of impurities (column 5, lines 53-56), and because Lemmens teaches the use of magnesium stearate as an optional ingredient (column 6, lines 25-29).

The Applicants respectfully traverse this rejection. Lemmens teaches away from the present invention's requirement of a lubricant that does not contain magnesium.[1] Lemmens teaches that decreasing the amount of magnesium stearate in amlodipine maleate formulations leads to an increase in the undesirable impurity amlodipine aspartate.

Lemmens provides numerous working examples. In the working examples, where formulations containing 0.5% magnesium stearate were compared to formulations containing 1% magnesium stearate, the formulations containing the lower amount of magnesium stearate generally produced more amlodipine aspartate. See, e.g., the table spanning columns 11 and 12. In that table, at 3 months, formulations A and B, each containing 1% magnesium stearate, produced 0.26% and 0.29% amlodipine aspartate, respectively. Formulations J and K, each containing 0.5% magnesium stearate, produced 0.46% and 0.40% amlodipine aspartate, respectively. At six months, the results were: A and B, 0.46% and 0.39% amlodipine aspartate, respectively; J and K, 0.64% and 0.54% amlodipine aspartate, respectively.

One of ordinary skill in the art, upon reading these disclosures, would have been led away from decreasing the amount of magnesium stearate further and thus would have been led away from the present invention.

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[1] Present claim 1 is actually broader in that claim 1 is directed to a lubricant that does not contain alkaline-earth metal ions and claim 3 specifies that the alkaline-earth metal ion is calcium. Lemmens does not discuss alkaline-earth metal ions in general. To the extend Lemmens is relevant to claims 1 and 3, it is believed that the arguments discussed herein are applicable to claims 1 and 3 as well.

A further teaching away from the use of a lubricant that does not contain magnesium is found in Canadian Patent Application No. 2,390,636 (CA 2,390,636). CA 2,390,636 is directed to the problem of the formation of amlodipine aspartate in amlodipine maleate formulations (see page 1). Yet CA 2,390,636 states that its preferred lubricant is magnesium stearate (see page 4, 4th paragraph) and the only lubricant used in the working examples of CA 2,390,636 is magnesium stearate.

Furthermore, Lemmens teaches away from those present claims that recite that the pH is about 5.1 (claims 10, 17, 34, 42, 52, 55, 57, 59, 61, and 63), about 5.0 to about 5.4 (claim 16), or about 5.0, about 5.1, about 5.2, or about 5.3 (claims 54, 56, 58, 60, and 62). Lemmens states that the pH must be between 5.5 and 7.0. See column 4, lines 60-64:

> Excipients having a pH effect can also be used. The pH of these excipients must be taken into account in developing the pharmaceutical composition so that the overall pH of the pharmaceutical composition falls within the range of about 5.5 to 7.0. [underscoring added]

See also column 2, lines 65-66: "Below a pH of about 5.5, other degradation reactions tend to be encouraged ..."

The Office Action referred to the Lemmens disclosure at column 5, lines 53-56, which reads as follows:

> For example, a pharmaceutical composition comprising amlodipine maleate and microcrystalline cellulose as the only excipient has been shown to provide good stability against the formation of impurities.

The Applicants wish to point out that all the present claims require the presence of a lubricant. The composition described in the passage above does not contain a lubricant ("microcrystalline cellulose as the only excipient"). Thus, this passage does not

suggest the present claims and, to the extent it is relevant, can be viewed as teaching away from the use of lubricants, and thus as teaching away from the present claims.

The same consideration applies to the Lemmens disclosure at column 6, lines 26-29, which reads as follows:

> A blend that comprises amlodipine maleate, microcrystalline cellulose and/or calcium phosphate, and optionally sodium starch glycollate and/or magnesium stearate may be useful in forming a tablet by direct compression.

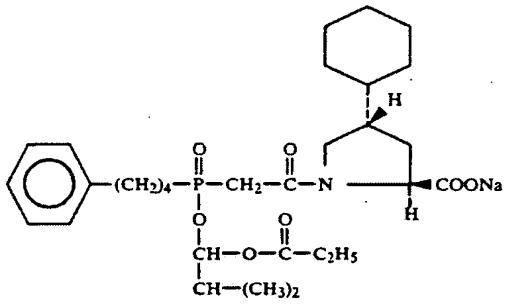
If this passage is viewed as disclosing a blend that does not contain magnesium stearate but does contain all or some of the other listed ingredients, such a blend would not be a formulation that contains a lubricant. Thus, this passage also does not make obvious the present claims.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 1-6, 13-30, 35-37, 39, 43-48, and 53 were rejected as being obvious over Lemmens in view of U.S. Patent No. 5,006,344 (Jerzewski).

The Applicants respectfully traverse this rejection. Jerzewski is directed to the antihypertensive agent fosinopril. Fosinopril and amlodipine have very different chemical structures. The difference in chemical structure between these two antihypertensive agents makes the disclosures of Jerzewski irrelevant to the present invention.

A major problem encountered with the use of amlodipine maleate is the formation of amlodipine aspartate. This problem cannot occur with the use of fosinopril. It is the occurrence of a Michael addition reaction between amlodipine and maleic acid that gives rise to the production of amlodipine aspartate. This Michael addition reaction occurs via the reaction of the amino group of amlodipine with the alpha carbon of maleic acid (see U.S. Patent Application Publication No. 2003/0180354, paragraph [0061]). Fosinopril lacks such an amino group. See Jerzewski, col. 1, ll. 40-51, where the following structure for fosinopril is disclosed:



Thus, even if fosinopril were formulated as a maleate salt, it would not be expected that the formation of fosinopril aspartate would be a problem. Therefore, one of ordinary skill in the art would not be motivated to combine Jerzewski with Lemmens since the teachings of Jerzewski would not be viewed as being helpful in connection with the problems addressed by Lemmens.

Furthermore, Jerzewski does nothing to counter the teachings away of Lemmens and CA 2,390,636 with respect to using a lubricant that does not contain magnesium or with respect to pH.

If must be kept in mind that the Applicants' invention is not simply the combination of amlodipine with a lubricant that does not contain magnesium. The Applicants' invention is directed to the combination of amlodipine maleate with a lubricant that does not contain magnesium. When one considers that amlodipine maleate was well known in the art and was well known to have significant drawbacks because of the production of amlodipine aspartate, it is evident that choosing the category of lubricants that do not contain magnesium for combination with amlodipine maleate, in order to overcome those well known problems of amlodipine aspartate, was not simply a matter of routinely or mechanically choosing from among the set of known pharmaceutical lubricants. Instead, the Applicants' discovery represents a true inventive advance in the art, requiring keen chemical insight beyond the reach of the ordinary artisan.

That the Applicants' solution to the amlodipine aspartate problem was non-obvious can be appreciated by considering the fact that Pfizer, one of the world's most successful pharmaceutical companies, was faced with exactly the same problem during the development of its amlodipine product Norvasc®. After having invested years of effort and many millions of dollars in developing amlodipine maleate to the stage of human clinical trials (see Lemmens, col. 1, l. 56, to col. 2, l. 4), Pfizer, faced with the same amlodipine maleate problem the Applicants addressed and solved, gave up and started over with a new salt.

It is not denied that the prior art included certain pharmaceutical lubricants that do not contain magnesium. But the prior art contains no suggestion to try the use of lubricants that do not contain magnesium to overcome the amlodipine aspartate problem,

and certainly the prior art does not provide a reasonable expectation of success for overcoming that problem.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 7-12, 31-34, 38, 40-42, and 49-52 were rejected as being obvious over Lemmens in view of Jerzewski and U.S. Patent No. 5,674,529 (Marder).

In this rejection, Marder is added to Lemmens and Jerzewski for the purpose of showing that the prior art included the use of hydrogenated castor oil as a pharmaceutical lubricant. This is no more than has already been acknowledged by Applicants. The prior art includes the use of pharmaceutical lubricants that do not contain magnesium.

Even if it is assumed, for the sake of argument, that there was motivation to combine one of the known pharmaceutical lubricants that do not contain magnesium (such as the hydrogenated castor oil of Marder) with amlodipine maleate, the Applicants have demonstrated that such a combination leads to unexpected results. In view of the teachings of Lemmens that decreasing the amount of magnesium stearate leads to increased production of amlodipine maleate, the Applicants' discovery that using a lubricant that does not contain magnesium leads to very low levels of amlodipine aspartate must be considered unexpected. Thus, the addition of Marder to Lemmens and Jerzewski does not make the present claims obvious.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 7-12, 31-34, 38, 40-42, and 49-52 were rejected as being obvious over Jerzewski in view of U.S. Patent Publication No. 2003/0180354 (Chakole).

As discussed above, the prior art (Lemmens and CA 2,390,636) teach away from the present invention. Also as discussed above, Jerzewski has essentially no relevance to the problem addressed by the present invention. That Jerzewski might be directed to an antihypertension agent is no matter. What mattered in terms of the problem the prior art faced with respect to amlodipine maleate was peculiar to the chemical structure of amlodipine, not the fact that amlodipine is an antihypertensive agent. Fosinopril, the subject of Jerzewski, does not share the chemical structure of amlodipine (i.e., the amino group) that allows amlodipine to combine with maleic acid via a Michael addition to produce amlodipine aspartate. Thus Jerzewski does not negate the teachings away of Lemmens and CA 2,390,636.

Chakole also does not negate the teachings away of Lemmens and CA 2,390,636. Rather than teaching that one should combine amlodipine maleate with a lubricant that does not contain magnesium, Chakole teaches a preferred embodiment, a more preferred embodiment, and a still more preferred embodiment that all contain a lubricant that contains magnesium (see paragraphs [0017], [0018], and [0019]). Also, the table between paragraphs [0064] and [0065] discloses formulations of amlodipine maleate that contain three different amounts of magnesium stearate. Only the formulation with the highest amount gives tablets without sticking. Sticking was a known problem of amlodipine maleate formulations (See Lemmens, col. 6, ll. 34-40). Accordingly, one of ordinary skill

in the art would have been led away from the use of low amounts of magnesium stearate by this disclosure of Chakole, in order to avoid sticking problems. Thus, Chakole reinforces the teachings away of Lemmens and CA 2,390,636 with respect to the use of lubricants that do not contain magnesium.

It should be noted that Chakole does not negate the teachings away of Lemmens with respect to pH. The only place in Chakole where the pH of an amlodipine maleate formulation is disclosed occurs at paragraph [0048] where a pH of 6.95 is disclosed. This reinforces the teaching of Lemmens that the pH should be between 5.5 and 7.0 and teaches away from those of the present claims that recite pH values.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 7-12, 31-34, 38, 40-42, and 49-52 were rejected as being obvious over Jerzewski in view of Chakole and Marder.

As discussed above, Jerzewski and Chakole do not negate the teachings away from the present invention of Lemmens and CA 2,390,636. Marder also does not negate these teachings away because Marder makes no mention of the problem of the formation of amlodipine aspartate in formulations of amlodipine maleate. Marder merely discloses the use of certain pharmaceutical lubricants in compositions unrelated to amlodipine maleate.

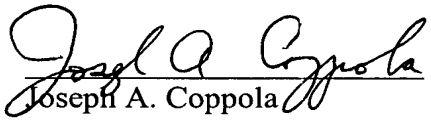
In view of the above, it is respectfully requested that this rejection be withdrawn.

The time for responding to the Office Action was set for June 9, 2007. Therefore, it is believed that this response is timely. If this is in error, please treat this response as containing a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this paper and charge any corresponding fees to Kenyon & Kenyon's Deposit Account No. 11-0600.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon LLP's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully submitted,

Dated: JUNE 7, 2007



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